PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 21 March 2001 (21.03.01)	
International application No. PCT/IL00/00420	**Applicant's or agent's file reference** 131,074 PCT
International filing date (day/month/year) 18 July 2000 (18.07.00)	**Priority date** (day/month/year) 23 July 1999 (23.07.99)
Applicant DOMB, Abraham, J.	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

11 February 2001 (11.02.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Charlotte ENGER
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

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Date of mailing (day/month/year) 20 March 2001 (20.03.01)	
International application No. PCT/IL00/00420	**Applicant's or agent's file reference** 131,074 PCT
International filing date (day/month/year) 18 July 2000 (18.07.00)	**Priority date** (day/month/year) 23 July 1999 (23.07.99)
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Form PCT/IB/331 (July 1992)

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search report

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(30) Priority Data:
131074 23 July 1999 (23.07.1999) IL

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(74) Agent: WOLFF, BREGMAN AND GOLLER; P.O. Box 1352, 91013 Jerusalem (IL).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/07486 A1

(54) Title: A BIODEGRADABLE POLYCATION COMPOSITION FOR DELIVERY OF AN ANIONIC MACROMOLECULE

(57) Abstract: The present invention provides a biodegradable polycation composition for delivery of an anionic macromolecule, comprising a polysaccharide chain having an amount of saccharide units ranging from 2 to 2000 and at least one grafted oligoamine per 5 saccharide units, wherein said oligoamine is selected from the group consisting of a linear, branched and cyclic alkyl amine having at least two amino groups.

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PATENT COOPERATION TREATY

RECD 01 NOV 2001

WIPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
131,074 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL00/00420	18/07/2000	23/07/1999
International Patent Classification (IPC) or national classification and IPC C08B37/00		
Applicant POLYGENE LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11/02/2001	30.10.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Gerber, M Telephone No. +49 89 2399 8528

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IL00/00420

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-6,10-58	as originally filed			
7-9,9a-9b	as received on	04/10/2001	with letter of	30/09/2001

Claims, No.:

1-18	as received on	04/10/2001	with letter of	30/09/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8, 10-13
	No:	Claims	1-7, 9, 14-18
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-18
Industrial applicability (IA)	Yes:	Claims	1-18
	No:	Claims	

2. Citations and explanations
   see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- **D1:** WO 98 01162 A (THE JOHN HOPKINS UNIVERSITY) 15 January 1998
- **D2:** DATABASE WPI Week 199533 Derwent Publications Ltd., London, GB; AN 1995-253643 XP002153583 & RU 2 027 190 A (AUTENSHLYUS A I), 20 January 1995
- **D3:** WO 93 25239 A (ADVANCED MAGNETICS IC) 23 December 1993
- **D4:** US-A-4 146 515 (PETER D. BUIKEMA ET AL.) 27 March 1979

1. Novelty

1.1. D3 refers to conjugates of arabinogalactan or derivatives thereof with therapeutic agents like DNA or antisense nucleic acid, for targeting the therapeutic agent into the cells possessing a asialoglycoprotein receptor which is capable of recognising the arabinogalactan derivative (see claim 28 and page 7, lines 7-14). Examples are given in which the positively charged poly-L-lysine arabinogalactan can cause some agents such as negatively charged nucleic acids like genes and antisense oligonucleotides to adhere by ionic exchange forces (see claim 9 and page 9, lines 4-15). A galactose oxidase treatment of arabinogalactan can be used to create aldehyde groups, which can be reacted with diamino compounds like ethylenediamine followed by reduction with sodium borohydride, for use for the attachment of therapeutic agents (see page 9, lines 18-24).

The subject-matter of **claims 1-7, 9 and 14-18** is therefore not novel over **D3** (Article 33(2) PCT).

1.2. D2 is concerned with a conjugate of polysaccharide antigen and polyethylene imine $-(NH-CH_2-CH_2)_x-[N(CH_2-CH_2-NH_2)CH_2CH_2]_y-$ used as a bonding linkage, useful as an immunosorbent for detecting streptococcal and pneumococcal infections.

The subject-matter of **claims 1, 3, 5, 6, 9, 14, 17 and 18** is not novel over **D2** (Article 33(2) PCT).

1.3. The subject-matter of **claims 8 and 10-13** is considered to be novel over the available state of the art (Article 33(2) PCT).

2. Inventive step

The features of **claims 9 and 11-14** are of common design procedure for the person skilled in the art. The subject-matter of these claims cannot therefore be considered as involving an inventive step (Article 33(3) PCT). These measures could only be deemed to be inventive if an unexpected effect was shown. However, the examples provided by the Applicant do not exhibit such an effect.

3. Industrial applicability

The subject-matter of present **claims 1-18** appears to comply with the requirements of industrial applicability as stipulated in Article 33(4) PCT.

4. form a stable enough complex with low and high molecular weight polynucleotides including therapeutic plasmids and antisense.
5. provide effective polymeric delivery system that result in a high transfection yield in a range of cells and in tissues.
6. can be reproducibly prepared at an affordable cost.

Another objective of this invention is to provide a controlled release of DNA in tissue or cell by complexing DNA with designed polymers that gradually de-complex and release the DNA or by incorporation of the complexed polynucleotides in a biodegradable matrix which will release the DNA in the site of insertion for periods of weeks and months.

Thus, according to the present invention there is provided a biodegradable polycation composition associated with an anionic macromolecule, said macromolecule being selected from the group consisting of a plasmid, an oligonucleotide, an antisense, a peptide, a protein, an anionic polysaccharide and combinations thereof, comprising:

a) a polysaccharide chain having an amount of saccharide units ranging from 2 to 2000; and

b) at least one grafted oligoamine per 5 saccharide units, wherein said oligoamine is selected from the group consisting of a linear, branched and cyclic alkyl amine having at least two amino groups and said oligoamine has a molecular weight of up to 2000 daltons.

In another preferred embodiment of the present invention said polysaccharide chain is selected from the group consisting of dextrans, arabinogalactan, pullulan, cellulose, cellobios, inulin, chitosan, alginates and hyaluronic acid.

In a further preferred embodiment of the present invention said saccharide units are connected by a bond selected from the group consisting of acetal, hemiacetal, ketal, orthoester, amide, ester, carbonate and carbamate.

In an even further preferred embodiment of the present invention said polysaccharide is a synthetic polysaccharide formed from the condensation of an aldaric acid and a diaminoalkane.

In a preferred embodiment of the present invention said grafted oligoamine is grafted to said polysaccharide chain by a bond selected from the group consisting of amine, amide and carbamate. In another preferred embodiment the oligoamine has the formula:

NH_2-[CH_2)$_x$-N-(R)-CH_2)$_y$-N-(R')-(CH_2)$_z$-]$_n$-NH_2

wherein x, y, z are an integer between 0 and 4 and x+y+z is between 1 and 4 and n is at least 1 when x+y+z=2 or more, or at least 2 when x+y+z=1 and wherein R and R' groups are H or an aliphatic side group of 1 to 6 carbons.

In a further preferred embodiment of the present invention said oligoamine is selected from the group consisting of spermine and derivatives thereof.

In an even further preferred embodiment of the present invention said oligoamine is selected from the group consisting of a linear and branched ethyleneimine oligomer having up to 10 ethylene imine units.

In an even further preferred embodiment of the present invention said oligoamine is selected from the group consisting of a a peptide consisting of up to 20 amino acids with at least 50% contain a cationic side group including, lysine, ornithine, and diphthamic acid.

In a preferred embodiment of the present invention said amphiphilic residue is selected from the group consisting of fatty chains, phospholipids, cholesterol derivatives, ethylene glycol oligomers and propylene glycol oligomers, wherein said ethylene and propylene glycol oligomers have a fatty chain block on one side.

In a further preferred embodiment of the present invention said amphiphilic residue is connected to said polysaccharide chain by a bond selected from the group consisting of an amine, amide, imine, ester, ether, urea, carbamate and carbonate.

In an even further preferred embodiment of the present invention said amphiphilic residue facilitates the crossing of the polycation through biological membranes.

In a preferred embodiment of the present invention said polycation composition is not toxic or immunogenic.

In an even further preferred embodiment, the composition of the invention further comprises a ligand for facilitating the binding of said composition to a predetermined type of cell or tissue.

It is a further an objective of the invention to provide a pharmaceutical composition comprising the composition described above, in combination with a pharmaceutically acceptable carrier.

It is a further an objective of the invention to provide a pharmaceutical composition comprising the composition described above, in combination with amphiphilic cationic and/or nonionic lipids and cationic and nonionic polymers generally used for nucleotide delivery transfection. Examples of lipids include DOTMA, DOTAP, DMRIE, GAP-DLRIE, DODHF, aklylated spermine, and other derivatives described in: G. Byk and D. Scherman, Exp. Opin. Ther. (1998) 8(9):1125-1141; D.A. Treco and R.F. Selden, non viral gene therapy, Molec. Med. Today, 1995, 1(7):299-348)

The present invention describes a range of biodegradable polycations based on grafted oligoamine residues on synthetic or a natural polysaccharides which are effective in delivering plasmids and antisense for a high biological effect. The grafting concept where side chain oligomers are attached to either a linear or branched hydrophilic polysaccharide backbone, allows two/three dimensional interaction with an anionic surface area typical to the double or single strand DNA chain. This type of flexible cationic area coverage is not available with non-grafted polycations or low molecular weight cations. Low molecular weight amines and their lipid derivatives such as the lipofectin and lipofectamine have a localized effect on the DNA which the degree of complexation is dependent on how these small molecules organized around the anionic DNA. Each molecule has to be synchronized with the other molecules at all times of the transferction process whereas when the oligoamines are grafted on a polymer they are already synchronized and each side chain helps the other side chains to be arranged to fit the anionic surface of the given DNA. By grafting the functional groups is an average distribution along a polymer chain at a certain distance between each other (for example,

grafting an oligoamine chain every one, two, three or four polymer unit may provide optimal complexation with various DNAs.

US 4,146,515 (D4) describes oxidation of starch and reacting it in bulk with epichlorhydrin-dimethylamine or ammonia to improve the industrial properties of starch. The product is cationic but is not a grafted oligoamine conjugated to a polysaccharide.

WO93/25239 (D3) to Advanced Magnetics describes a range of derivatives of arabinogalactran. In Example 10 page 19, there is described the treatment of AG with galactose oxiddase (GO). The reaction details are given including the purification process and determination of the number of aldehyde groups formed. The oxidation with the enzyme takes place at room temperature which yields 0.34 milliequivalents of aldehydes. This is an alternative method of oxidation of AG and is not related to an oligoamine conjugated to polysaccharides.

In example 6, page 17 of said publication, there is described the reaction between polylysine and arabinogalactan (AG) at a ratio of 500 mg polylysine and 100 mg of AG in the present of cyanoborohydride as reducing agent. The resulting product yield was 30 mg which represents a 5% yield. No date is given on the analysis of this product besides a comment that the product contains an amine and saccharide and has a molecular weight of 25,000. Under these reaction conditions in which AG was not oxidized and native AG was used, the chance for a chemical conjugation between polylysine and AG is very low as there are no or only a few aldehyde groups on AG that are available for a reductive amination reaction. Indeed, the negligible yield of 5% with no characterized product indicates that probably nothing was obtained in this reaction and the 5% material isolated was either polylysine contaminated with AG or AG contaminated with polylysine, the latter seeming more probable as native AG has a molecular weight of 25,000. Thus this example does

not teach or suggest to a person skilled in the art the formation of an oligoamine conjugated with polysaccharides.

WO 98 01162 (D1) describes the formation of Chitosan nanoospheres containing DNA complexed with the cationic groups of the native Chitosan. Page 17 and Figs 7 and 8 describe in detail the formation of the Chitosan nanospheres loaded with the DNA. Chitosan contains one amino group per saccharide unit as it is a polymer of glucose amine. This polymer is a polysaccharide with one amino side group which is not an oligoamine conjugated to a polysaccharide.

RU 2,027,190 (D2) describes a conjugate of polysaccaharide antigen and polyethylene imine as an immunosorbent for detecting streptococcal and pneumococcal infections. Said reference thus teaches an antigen which is chemically bound to a polysaccharide via a spacer which is a polyethylene imine and does not teach or suggest an oligoamine conjugated to a polysaccharide.

US 5,567,685 describes the conjugation of various oxidizable drugs to a polysaccharide, however, does not teach or suggest an oligoamine conjugated to polysaccharide.

WHAT IS CLAIMED IS:

1. A biodegradable polycation composition associated with an anionic macromolecule, said macromolecule being selected from the group consisting of a plasmid, an oligonucleotide, an antisense, a peptide, a protein, an anionic polysacharide and combinations thereof, comprising:
   a) a polysaccharide chain having an amount of saccharide units ranging from 2 to 2000; and
   b) at least one grafted oligoamine per 5 saccharide units, wherein said oligoamine is selected from the group consisting of a linear, branched and cyclic alkyl amine having at least two amino groups and said oligoamine has a molecular weight of up to 2000 daltons.
2. A biodegradable polycation composition according to claim 1, wherein said polysaccharide chain is selected from the group consisting of dextrans, arabinogalactan, pullulan, cellulose, cellobios, inulin, chitosan, alginates and hyaluronic acid.
3. A biodegradable polycation composition according to claim 1, wherein said saccharide units are connected by a bond selected from the group consisting of acetal, hemiacetal, ketal, orthoester, amide, ester, carbonate and carbamate.
4. A biodegradable polycation composition according to claim 1, wherein said polysaccharide is a synthetic polysaccharide formed from the condensation of an aldaric acid and a diaminoalkane.
5. A biodegradable polycation composition according to claim 1, wherein said grafted oligoamine is grafted to said polysaccharide chain by a bond selected from the group consisting of an amine bond, an amide bond and a carbamate bond.
6. A biodegradable polycation composition according to claim 1, wherein said oligoamine has the formula:

   $NH_2\text{-}[CH_2)_x\text{-}N\text{-}(R)\text{-}CH_2)_y\text{-}N\text{-}(R')\text{-}(CH_2)_z\text{-}]_n\text{-}NH_2$

wherein x, y, z are an integer between 0 and 4 and x+y+z+ is between 1 and 4 and n is at least 1 when x+y+z=2 or more, or at least 2 when x+y+z=1 and wherein R and R' groups are H or an aliphatic side group of 1 to 6 carbons.

7. A biodegradable polycation composition according to claim 1, wherein said oligoamine is a peptide of up to 20 amino acids with at least 50% of the amino acid are cationic including lysine, ornithine, and diphthamic acid.
8. A biodegradable polycation composition according to claim 1, wherein said oligoamine is selected from the group consisting of spermine and derivatives thereof.
9. A biodegradable polycation composition according to claim 1, wherein said oligoamine is selected from the group consisting of a linear and branched ethyleneimine oligomer having up to 10 ethylene imine units.
10. A biodegradable polycation composition according to claim 1, having an amphiphilic residue wherein said amphiphilic residue is selected from the group consisting of fatty chains, phospholipids, cholesterol derivatives, ethylene glycol oligomers and propylene glycol oligomers.
11. A biodegradable polycation composition according to claim 11, wherein said ethylene and propylene glycol oligomers have a fatty chain block on one side.
12. A biodegradable polycation composition according to claim 11, wherein said amphiphilic residue is connected to said polysaccharide chain by a bond selected from the group consisting of an amine, amide, imine, ester, ether, urea, carbamate and carbonate.
13. A biodegradable polycation composition according to claim 11, wherein said amphiphilic residue facilitates the crossing of the polycation through biological membranes.
14. A biodegradable polycation composition according to claim 1, wherein said polycation composition is not toxic or immunogenic.

15. A biodegradable polycation composition according to claim 1, wherein said composition further comprises a ligand for facilitating the binding of said composition to a predetermined type of cell or tissue.
16. A biodegradable composition according to claim 1, in combination with cationic and nonionic lipids or polymers for cell transfection.
17. A pharmaceutical composition, comprising the composition of claim 1, in combination with a pharmaceutically acceptable carrier.
18. A pharmaceutical composition according to claim 17, wherein the pharmaceutically acceptable carrier is an amphiphillic cationic and/or non-ionic lipid and cationic and non-ionic polymers generally used for nucleotide delivery

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
131,074 PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IL 00/00420	18/07/2000	23/07/1999
Applicant		
POLYGENE LTD. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 00/00420

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C08B37/00 A61K47/36 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C08B A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 01162 A (THE JOHN HOPKINS UNIVERSITY) 15 January 1998 (1998-01-15) page 17, line 20 - line 21; figures 7,8 ---	1-18
Y	DATABASE WPI Week 199533 Derwent Publications Ltd., London, GB; AN 1995-253643 XP002153583 & RU 2 027 190 A (AUTENSHLYUS A I), 20 January 1995 (1995-01-20) abstract ---	1-18
Y	WO 93 25239 A (ADVANCED MAGNETICS IC) 23 December 1993 (1993-12-23) example 10 --- -/--	1-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 November 2000	01/12/2000

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INTERNATIONAL SEARCH REPORT

International Application No
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